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Semi-Annual Progress Report

(NAVY RESEARCH SECTION)

Title of Project: The Synthesis of Peptides

Period Covered: July 1, 1952 - December 31, 1952

Date of Submission: December 30, 1952

Principal Investigator: Joseph S. Freton

Contractor: Tale University

Subtask No: NR 12h-951

Contract No: Monr 2h2(00)

As indicated in my previous Semi-Annual report, work on this project was to be resumed on August 1, 1952 since we had succeeded in securing the services of Br. Louis A. Cohen. Funds are currently available for the support of Br. Cohen's work until March 31, 1953. An application for the renewal of the grant until June 30, 195h was submitted on March 31, 1952.

During the past five months, Dr. Coben and I have conducted work on (1) the synthesis of peptides containing series and phosphoserine residues; (2) the use of trifluoroscetic anhydride in peptide synthesis; (3) the use of smino acid thiol esters in peptide synthesis.

reptides of Serine and Phosphoserine - Attention was first directed to the development of a satisfactory method for the synthesis of phospho-Lserine, since the procedures in the literature leave such to be desired.

Attempts to obtain this material by treatment of the copper complex of serine with POCl<sub>3</sub> or diphenylphosphoryl chloride (followed by hydrogenolysis) were unsuccessful, possibly because the copper cholate involves the serine hydroxyl group. For this reason, emphasis is now being placed on the

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phosphorylation of carbobencoxy-L-serine benzyl ester, which has been obtained for the first time by the carbobencoxylation of L-serine benzyl ester. Of a number of methods tested, the best procedure for the preparation of the last named compound involves the use of benzyl alcohol - hydrogen chloride.

preliminary experiments have been performed on the synthesis of serime peptides in which hydroxyl group of serime is involved in an ester linkage with the carboxyl group of another smino acid. For this work, the carbobenzoxy-L-serime benzyl ester is a valuable starting material, since it can be treated with the acid chloride of a carbobenzoxyazino acid to give a coupling product that should yield the desired 0-peptide on hydrogenolysis. Some difficulty has been encountered in performing the coupling reaction to give a pure product, and further work is necessary.

The synthesis of peptides of L-serine has been improved by modification of the procedures described in the literature. It is planned to subject compounds such as carbobensoxy-L-seryl-L-alanine bensyl ester to phosphorylation with dibensylphosphoryl chloride and to obtain the phosphoserine peptides by hydrogenolysis of the coupling product.

Development of New Reagents for Peptide Synthesis - Experiments were conducted to examine the possible usefulness of trifluoroscetic acid anhydride for the synthesis of peptides. Thus, carbobenzoxyglycine and the anhydride were allowed to react, and the mixed anhydride treated with an amino acid ester. However, under the conditions employed, the yields of desired product were inferior to those obtained by older methods. It may

be that with other acylemino acids, the reaction with trifluoroacetic anhydride may be more satisfactory; such experiments are planned.

The use of thiol esters of acylamino acids for peptide synthesis has recently been reported in the literature. Although we performed preliminary experiments along this line prior to the appearance of this report,
our efforts in this direction have been suspended so as not to duplicate
studies known to be conducted elsewhere.

Respectfully submitted,

Joseph S. Fruton

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